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The UK's Search for an Incapacitating ('Non-Lethal') Chemical Agent in the 1960s*

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Fig.1
Transmitter on the Head of a Cat.

January, 2006

Introduction

As the revolution in the life sciences progresses it is becoming ever more difficult to differentiate between chemistry and biology. When thinking about weapons agents, therefore, it is important to consider a biochemical threat spectrum rather than separate chemical and biological threats. A biochemical threat spectrum ranges from classical lethal chemical weapons agents through dangerous industrial chemicals to mid-spectrum agents such as toxins and bioregulators and on to traditional and genetically-modifed biological agents.[1]

Bioregulators are chemical signalling molecules within the organism such as neurotransmitters in the nervous system, hormones in the endocrine system, and cytokines in the immune system.[2] Such chemicals are appropriately covered by the Chemical Weapons Convention (CWC), but they may also be considered to be included - by the term "toxins" in Article I - in the prohibition in the Biological and Toxin Weapons Convention (BTWC). Certainly, concerns about bioregulators have been raised in the background papers on scientific and technological developments prepared for successive review conferences of the BTWC.[3]

It is well known that a number of states have pursued programs intended to develop agents with specific effects on the nervous system of a quite different order from traditional (irritant) riot control agents. For example, the United States weaponized BZ in the 1960s[4] and Iraq was reported to have a psychoactive agent, Agent 15, in the 1990s.[5] Furthermore, an agent (or agents) of this type were used to break the Moscow theatre hostage crisis in late 2001.[6] The intention here, however, is to concentrate on the program carried out in the United Kingdom during the 1960s, since much of the relevant official documentation has recently become available.

Some of this material has already been subjected to extensive research, for example in the detailed chronology, *Disabling Chemical Weapons*, produced by Perry Robinson,[7] and in the book *Gassed* by Evans,[8] where one chapter deals with the experimentation on human subjects with such materials. What I wish to do here is to concentrate on the questions of what the scientists were trying to do and what they achieved.

Before proceeding, however, it is necessary to be clear that, as Carter and Pearson explained in their history of British chemical weapons capabilities, the UK at this time did have an offensive program.[9] The relevant minutes of the Cabinet Defence Committee meeting of May 1963, chaired by Prime Minister Harold Macmillan, agreed to a proposal from the Minister of Defence which included:[10]

> "an increase in research and development on lethal and incapacitating chemical agents and the means of their dissemination (£0.64 million over five years),[and] limited production of a chemical agent (£1.5 million over five years)"

However, it was also agreed that "the agents produced as a result [of the program] should not be deployed at present." It appears that the program came to a halt within about a

decade and that no significantly usable incapacitants were discovered. This gives us a quite constrained period of activity, therefore, to examine.

The Program

The United States had begun investigating potential incapacitating agents in the early 1950s and their program was much larger than that carried out in the UK. The chapter on "Incapacitants" in the US *Textbook of Military Medicine* of 1995 states:[11]

> "Virtually all drugs whose most prominent effects are psychological or behavioral (sometimes referred to as psychochemicals) can be classified into four fairly discrete categories: stimulants, depressants, psychedelics, and deliriants"

Examples of these different types of drugs are shown in Table 1.

Table 1: Psychochemical Agents*

Stimulants

Amphetamines (phenylethylamines), cocaine, caffeine, nicotine.

Depressants

Barbiturates, morphine, morphine analogs, antipsychotic (neuroleptic) major tranquilizers such as haloperidol and other butophenones.

Psychedelics

D-lysergic acid diethylamide (LSD) and analogs, psilocybin, ibogaine, harmine, synthetic psychedelic drugs such as MDMA (ecstasy), phencyclidine.

Deliriants

Atropine, scopolamine and other anti-cholinergics such as BZ, many other drugs in large overdoses.

From reference[11]

Available Data

The center of the British work, of course, was Porton Down in Wiltshire, then called the Chemical Defence Experimental Establishment (CDEE). A series of major Porton Technical Papers from that period have become available at the Public Record Office in London.[12] One point that is immediately obvious is that intensive work on incapacitants preceded the Cabinet decision of May 1963. This is hardly surprising since the UK had been informed of the ongoing US program through the Tripartite Conferences on Toxicological Warfare and at the Thirteenth Conference in September 1958[13] it had been agreed that all three countries [the US, the UK, and Canada] should concentrate on the search for incapacitating and new type lethal agents." At the Fifteenth Meeting,[14] held at Porton in September 1960, a recommendation was also made that there should be "the granting of highest priority in agent-munition programmes to research and development of incapacitating agent systems, together with development of user concepts." Clearly then, to properly understand the British program, it is necessary to consider work carried out prior to the Cabinet decision.

It is possible to gain an overview of the evolution of the program from a series of bi-annual and annual reports and commentaries on all work at Porton - and reports to the Tripartite Conferences - that are available in the Public Record Office. Additionally, the listing of collected papers from the Chemical Defence Experimental Establishment for 1962[15] and 1964[16] detail three publications[17,18,19] in the open literature which are clearly related to the ongoing studies of incapacitants at Porton. Furthermore, as early as 1964, there were press reports of work on LSD at Porton,[20] and of studies of the effects of LSD on troops by 1969.[21]

This rather open view of the work carried out in the program could possibly be connected with a comment made by an official on the Chemical Defence Advisory Board-Annual Review for 1964 to the effect that:[22]

> "we understand US and UK scientific opinion is that it is not feasible to produce an incapacitating agent which will not cause some harmful or even lethal direct effects."

Whatever the reason, a series of papers by the same Porton authors as for the Technical Papers were published in the open literature during the 1960s and 1970s. There was also a collection of papers from a symposium held at Porton and co-edited by R. W. Brimblecombe in 1972,[23] and several books by the same author in the early 1970s.[24,25,26]

The work at Porton, and any associated extra-mural research elsewhere was reported to a series of secret committees. These committees, in addition to civil servants and military personnel, had numerous eminent British civil scientific specialists serving who are readily recognisable in the relevant copies of the yearly *Who's Who*. For the period of interest here, particularly from April 1960, the Advisory Council on Scientific Research and Technical Development had overall responsibility:[27]

> "To consider and initiate new proposals for research and development and to review research and development in progress in War Office establishments and extra-murally, in relation to the most recent advances in scientific knowledge."

A number of Boards reported to the Council, and of particular interest here is the Chemical Defence Advisory Board which had:[28]

> "To review and advise on problems concerning chemical warfare research and development carried out in the War Office and extramurally."

In its turn, this board had several committees: the Biology Committee, the Chemical Committee, the Defensive Equipment Committee, the Offensive Evaluation Committee and the Physics and Physical Chemistry Committee. In 1961 it also had an Enzyme panel. In late 1964 it was decided that from 1 April, 1965:[29]

> "(1) The Enzyme Panel be disbanded;
> (2) a new Biology Committee be appointed to be concerned with the basic medical sciences;
> (3) an Applied Biology Committee be set up to be concerned with the applied sciences (medicine, psychology, etc.)"

The minutes of many of the meetings of the Council, Board and Committees have been made public. Additionally, many reports presented to these bodies on the progress of the research on incapacitants have also been released. However, as the subject of human testing has been amply reviewed by Evans,[30] I have not concentrated on that issue here.

Previous Research

The chapter of the US text on military medicine dealing with incapacitants concluded in the mid-1990s that only one group of chemicals - within the category of those producing delirium - were likely to be used as military incapacitating agents. This group of chemicals are known as anticholinergics because they block the effect of the neurotransmitter chemical acetylcholine at one type of synapse -muscarinic-(that is, at synapses where the normal effect of acetylcholine is mimicked by muscarine,an extract from a mushroom).[31] One particular chemical from this group - known as BZ (3-quinuclidinyl benzilate) - was weaponised by the United States during the 1960s[32] and its mode of action is widely understood.[33]

There have been two previous studies of aspects of the British search for an effective incapacitant during the 1960s. In 1997 Caitriona McLeish analysed the problem of governance of dual-use technologies and within that subject considered the work of CDEE on TL2636, a derivative of thebaine.[34] In 2001 Kathryn McLaughlin considered the British work on LSD (lysergic acid diethylamide) in a detailed case study.[35] McLeish records how British post-war work initially concentrated on the newly discovered lethal nerve agents and then on how the new riot control agent CS (a physical irritant) became important "in aiding a more orderly retreat from the Empire." Together with growing US

enthusiasm and the successful use of new drugs in psychiatry, she argues, this raised interest in finding yet more powerful mental incapacitants (psychochemicals) that altered the target's state of mind and thus physical performance. As in the United States, the British military search for such incapacitants was assisted by information from industry and Mcleish explains how TL2636 was provided by an industrial company. The substance, which has pharmacological effects similar to those of morphine, was tested an animals and then on humans, but she suggests that cuts in British defence expenditure in the mid-1960s precluded any move to weaponisation.

Kathryn McLaughlin gives a detailed account of the development of British policy in the 1950s and 1960s and then focuses her attention particularly on the work on LSD. She describes how LSD acts at certain types of serotonin (5-hydroxytryptamine) neurotransmitter synapses and "sets off a complex cascade of events within the central nervous system." It was of considerable interest because it was effective at low dosages and had a very high ratio between effective incapacitating and lethal doses. McLaughlin explains that whilst LSD met many of the criteria required for an effective incapacitant, it was then very expensive to manufacture and extremely variable in the behavioural effects it produced. British research included laboratory tests on animals and humans and three major field trials involving volunteers.

The tests and trials are described in some detail by McLaughlin. She notes that LSD was rejected not only because of the expense of production and the unpredictability of its effects but also because it was difficult to aerosolise and the effective dose by inhalation was quite high. What is obvious from both of these accounts is that a determined effort was made in the UK to find an effective incapacitant.

The next section uses the publicly available documentation to attempt a year-by-year account of the development of the whole program.

Annual Accounts

Before 1963

Whilst work at Porton in the mid-1950s was still much concerned with defence against the nerve agents[36] and development of the CS riot control agent,[37] studies of the physiological effects and mechanism of action of LSD had commenced by 1956.[38] Systematic work on new agents as a whole was underway in 1957 when a working party was set up at CDEE. This working party had already held twelve meetings by the time its survey of the literature for leads to the development of new agents was discussed by the Chemistry Committee in March 1959.[39] The survey itself had eleven sections: review of the deliberations and conclusions of the U.S. Advisory Committee; drugs causing mental derangement; screening tests for psychotomimetic drugs; antibiotics; venoms; specific enzyme inhibitors; neuromuscular blocking agents; ganglion blocking agents; alkaloids; cardioactive steroids; and interim conclusions. Both lethal and incapacitating new agents were being sought, but in regard to incapacitating agents it was suggested that investigations should begin on indolealkylamines and atropine-like substances if

satisfactory testing methods could be developed. This was agreed by the committee, and reported on up to the Advisory Council on Scientific Research and Technical Development.[40] Yet at the end of 1960 it was noted at the Third Meeting of the (reconstituted) Advisory Council on Scientific Research and Technical Development that the search for new agents had been going on for some years without any clear lead emerging and that:[41] "[T]he present indication was that it would be very difficult to find an agent with a worthwhile incapacitating effect which would not result in either death or permanent injury."

In regard to agents that might potentially cause incapacitation by interfering with the functions of the central nervous system, a wide range of possibilities were already being investigated by 1960. Dr. Downing reported on the ongoing work on indoles to the Chemistry Committee in late 1959.[42] He also introduced a paper to the committee in mid-1960 updating the work on indoles and also mentioning work on analogues of tremorine amongst other agents.[43] The annual review of the Chemical Defence Advisory Board for 1961 noted ongoing work on tryptamines and indoles and on agents that might disturb the balance of gamma amino-butyric acid in the brain. The report also noted the fact that the industrial liaison program visits to industrial firms were proving to be valuable and approximately thirty firms had been visited.

One of the major problems faced by the investigators was how to screen the potential agents in animal tests and to have some means of moving on from tests on animals to operational agents[45]--that is, to testing on humans beings. Despite the difficulties, the effects of injecting the pyrogen Pyrexol were reported to have been tested on 27 men in 1959,[46] and there was clearly a determination to move on to more human testing. Human testing of psychotomimetic substances was started in late 1961.[47] One reason for the urgency was an increasing perception of the need for a militarily useful chemical incapacitant. As the Operational Evaluation Committee noted in early 1960:[48]

> "To satisfy the operational requirements, apart from CS which is probably unsuitable because of the short period of incapacitation, there were no other substances which could yet be recommended as military incapacitating agents."

The scientific difficulties faced by the investigators remained formidable.

The United Kingdom's approach to these difficulties was set out in a discussion paper for the Fifteenth Tripartite Conference in 1960.[49] This paper suggested that there were two main lines of approach in the search for new agents: the biochemical and the pharmacological. In the biochemical approach, "the possibility of interfering with various essential systems within the body is considered." The pharmacological approach was considered more empirical and "consists in searching for drugs with effects which may be incapacitating." A third "physiological" approach involved looking at various body functions and how they might be disrupted. Crucially, the paper pointed out:

> "Ideally, the best possible method for preparing a new agent with a given action would be to design a molecule which would have this specific type of action."

However, it noted that "*knowledge of structure-activity relationships is not sufficiently exact for this to be possible*" (emphasis added). Thus another approach was an entirely empirical one in which a wide-ranging literature survey might "perhaps by chance" throw up promising leads. Given the importance of knowledge of structure-activity relationships for the design of new agents, the obvious attraction of compounds with structural or functional relationships to the small number of neurotransmitters then known is understandable.

Transmission of information within the individual cells (neurons) of the nervous system is by electrical means, but transmission between neurons, or between neurons and effector organs (such as muscles) is predominantly by chemical means. We now know that the neurotransmitter chemical has to be specific for the receptor sub-type at the junction (synapse) and that a variety of mechanisms ensure that the transmitter acts only for the precise period required.[50] The investigators were obviously interested in muscarinic acetylcholine synapses because they knew how nerve agents prevented destruction of the transmitter by binding to the enzyme that normally destroyed it and that atropine could be used to block the neuronal receptors and thus help to avoid the consequences of excess acetylcholine. They also knew something about the operation of monoamine neurotranmitters such as epinephrine, norepinephrine and dopamine (catecholamines), and serotonin (5-hydroxytryptamine) which is an indoleamine. The initial decision to concentrate work on atropine-like substances and indoleamines is therefore understandable, as is the interest in gamma aminobutyric acid which was also known as a neurotransmitter.

Against that background it is not surprising that studies were made of the inhibition of monoamine oxidase and presented in a detailed series of Porton Technical Papers during the late 1950s and 1960.[51] This enzyme was thought to "play an important role in the metabolism in the brain of endogenous catecholamines and indolealkylamines such as noradrenaline [norepinephrine] and 5-hydroxytryptamine" so it was hoped to find ways of severely interrupting its function and thus causing incapacitating effects.

The research program underway at Porton in the early 1960s can be clearly visualised from the series of Porton Technical Papers for 1961 and 1962. Three papers addressed the problem of biological testing of incapacitants in animals. The first of these reviewed available testing methods,[52] the second assessed the results, in such tests, of using drugs with known effects on humans[53] and the third considered the screening of new compounds using the available tests.[54] The tests used were of four types: firstly, general tests such as the effect on body temperature; then tests for physical incapacitation such as reduced ability to climb an inclined rod; thirdly there were a series of simple behavioural tests such as the effect of a drug on the way on animal behaved when put into a relatively open space (Hall's Open Field Test); and finally, more complex measures of the effects of a drug on the results of a learned avoidance test. Such more complex tests were the subject of a further paper in mid-1962.[55]

At the same time a variety of potential agents such as simple peptides,[56] indoles and tryptamines,[57] and N-N-dialkyltryptamines[58] were being synthesised and subjected to screening.[59] Sometimes, also, as discussed by McLeish,[60] the industrial liaison program produced a chemical thought worthy of further intensive study.[61] A detailed report on the then current position in the search for new agents, and future intentions for the research, was given at the Chemistry Committee's 42nd meeting in 1962.[62] In regard to "Incapacitating Compounds," this reported work on indoles and tryptamines, tremorine and derivatives, substituted hydroxylamines and hydrazines (to interfere with gamma aminobutyric acid metabolism), pyrroles, benzimidazoles (which have an analogous structure to indoles) and a variety of irritants and miscellaneous products.

Dr. Downing also gave a review of the work on incapacitating agents to the ninth meeting of the Offensive Evaluation Committee in January 1962.[63] He stated that there were three lines of investigation: systematic literature review; liaison with industrial laboratories and universities; and research stimulated at CDEE (Porton). The policy had been to explore the maximum number of possibilities and to keep the laboratory work to the minimum needed to determine whether a substance was of interest. Dr. Downing also noted that two major leads were being followed up in the United States. These were quinuclidinyl benzilate (EA2277/BZ) and tetrahydrocanabinol (EA1476/marihuana). He explained that whilst the US was concentrating on mental incapacitation, the UK was also interested in physical effects such as that produced by the oripavine derivative T.L.2636 (which in low doses caused nausea and vomiting and sensations similar to motion sickness).[64]

However, as the director of Porton, Mr. Haddon, explained to the Chemical Defence Advisory Board in May 1962,[65] for the past five or six years the work at CDEE had been guided by a policy directive "to study and develop means . . . to defend ourselves against chemical warfare" (that is, a defensive program). Now he reported on "the various signs that this somewhat restrictive policy directive would be changed" and that "CW with incapacitating agents would probably not be open to the same political objections [as lethal CW] and increasing research and development effort up to full weapon development was therefore favoured." In the new circumstances he anticipated CDEE would receive increased funding and increased staffing but in the meantime "they were re-arranging their research program to give increased emphasis to incapacitating agents and means for their dispersal."

1963

At the 53rd meeting of the Chemical Defence Advisory Board on 6th June 1963 Mr. Haddon noted,[66] in a discussion of "[N]ew agents research", that "CDEE now had a directive for the development of incapacitating agents, so they had been right to study these compounds." At the next meeting of the board a top secret paper on the UK's chemical warfare policy was tabled, but not circulated. It was stated that the services had formulated their new requirements for phase I (1964-1969) and some proposals had been put forward in regard to phase II (1969-1974).[67] Yet there were clearly problems, for example in obtaining suitable staff[68] to carry out the work and in obtaining sufficient

human volunteers for tests. Part of the program was clearly carried out not only through industrial liaisons, but also through extra-mural research contracts.[69]

The December 1963 report to the Chemistry Committee, on "[N]ew agent research" contained an interesting development in regard to the work on tremoram.[70] It stated that this compound had effects at muscarinic acetylcholine receptors and discussed the structural requirements necessary for it to have an effect at the receptor. Three Porton technical papers investigated these issues in considerable detail.[71,72,73] The December meeting also considered the preparation and properties of BZ. This had been the subject of a Porton Note which was based on information in US reports.[74] Whilst the search for new related compounds was being left to the United States, the UK was evaluating BZ and one related compound (EA3443) which was considered to be an important new finding.

1964

At a meeting of the Advisory Council in Nombember 1964[75] General Sir John Hackett stated that "it was very desirable to find a safe incapacitating agent. . . . General Staff Targets had been issued." The increased service interest in chemical warfare was also clear from the major troop exercise TUREEN[76] which was the first "for many years to include situations involving the use of chemical warfare."

In this situation the new agents search was clearly important. At the Chemical Defence Advisory Board's meeting in June 1964[77] there was a report of the 48th meeting of the Chemistry Committee. The report stated that:

> "There had been five papers on new agent research relating to psychotomimetic compounds and compounds acting on the central nervous system. These papers covered the preparation and testing of a number of variations of known active structures and represented a useful addition to knowledge."

One of these papers dealt with the search for pharmacologically active benzimidazoles.[78] The paper noted that studies of these compounds had been reported in three Porton Technical Papers (859, 895, 896). The compounds, which resemble tryptamines, were considered for possible effects on the central nervous system but the effects detected "were due to toxic action on the heart" and not on the central nervous system. Further work was therefore not contemplated, particularly as the French had become interested in this field of work.

The meeting of the Chemical Defence Advisory Board in October 1964 considered the CDEE annual report for the period ending 30th June 1964. The report on new agents stated that some 150 compounds had been screened during the year with some 10-15 per cent of these coming from industry or universities.[79] Particular note was made of work on compounds possessing muscarinic activity and on oripavine derivatives, while work on indoles and tryptamines also continued. At the UK's production site (Nancekuke) work

also continued on the problem of synthesising large enough quantities of compounds for testing.

More detailed figures are also available in the fourth of the series of Porton Technical Papers on *Biological Testing of Incapacitating Agents*.[80] During the period August 1961-December 1963 240 new compounds had been received for testing as potential incapacitating agents, and of these:

> "It is considered that two tryptamine derivatives, one pyrrole [related to indoles], one phthalimide, four oripavine derivatives, one hydrazine [which might inhibit monoamine oxidase], tremoram and three allied compounds, and three compounds of a miscellaneous nature"

warranted further study.

Also in 1964, two papers appeared in the open literature that were written by staff at Porton involved in the search for new incapacitating agents. [Dr. Downing had a major review of the literature on psychotomimetic compounds published whilst stationed at the British Embassy in Washington[81] and also co-authored a paper with Brimblecombe, Green and Hunt[82] on tryptamine derivatives in which their Porton Down CDEE address was given. As Mr. Haddon had pointed out in 1963,[83] staff were encouraged to publish in the open literature and "even if the application of work was classified, security difficulties could be overcome by employing suitable means of presentation."

1965

Difficulties with staff recruitment and retention, particularly in the medical division at CDEE, continued in 1965. A report to the Advisory Council[84] in April noted that "they had been unable recently to find medical staff to control the tests of incapacitating agents; as a result that work had had to be stopped." Yet the Council, in its annual report[85] for 1965, stressed the perceived importance of the work, "[W]e consider that experiments on this humane type of warfare should be pressed forward with all speed."

In introducing the CDEE report for 1964-1965 to the Chemical Defence Advisory Board, Mr. Haddon said that it dealt essentially with the first year of the expanded program:[86]

> "The original concept had been five years of steady expansion, the first two of which would be devoted to the recruitment of staff, the third to the acquisition of laboratory apparatus and equipment and the fourth and fifth to the development of more sophisticated equipment and techniques."

Interestingly, when the board visited CDEE in May 1965 one of the demonstrations provided was of the new neuropharmacology laboratory by R. W. Brimblecombe.[87]

The 50th meeting of the Chemistry Committee[88] was focused on the new agents program. Mr.Bebbington presented a review of the program[89] and made it clear in his presentation

that the New Agents Committee at CDEE was still in operation and making recommendations for further work. R. R. Hunt presented a review of CDEE work on indole derivatives from 1959-1964.[90] This paper noted that Downing, in 1959, concluded that at that time "the derivatives of indole were most likely to provide new compounds with high activity." The research on indoles had resulted in seven Porton Technical Papers (739, 892, 771 and 822, 770, 915 and one in preparation). However, because of "the limited incapacitating effect, at relatively high doses,of the simple tryptamines, and the higher lethality of the more active ring-substituted tryptamines" it was recommended that no further synthetic work should be carried out on simple indoles and tryptamines.

A further paper by R. W. Brimblecombe and D. G. Rowsell considered the interaction of muscarinic drugs with the post-ganglionic cholinergic receptor and supported the idea of a three point interaction between drugs and the receptor.[91] This paper was obviously related to a series of Porton Technical Papers (912, 913, 914) dealing with aspects of this topic, and a major paper by Bebbington and Brimblecombe[92] covering the same topic appeared in the open literature during the year.

The state of the program of chemical and medical research on new agents can be gained from a prepared summary of the CDEE annual report for 1964-1965.[93] This stated that about 150 compounds, mainly potential incapacitants, had been examined during the year. There had been a steady decline in the number of human volunteers for testing from 306 in 1962-1963 to 167 in the year of the report, but this had been offset to an extent by people volunteering for longer. The main lines of the intra- and extramural research described in the report are shown in Tables 2A and 2B. Work had also continued on finding better methods of assessing incapacitating effects, and the report noted that as many potential incapacitants were solids at normal temperatures research on dispersal mechanisms was being carried out as well.

As is evident from Table 2A, work with LSD25 included a small-scale field trial of its effects on trained troops.[94] The film of the exercise was shown at the first meeting of the new Applied Biology Committee in November 1965[95] and Mr. Haddon explained that the main questions of interest to CDEE were:

> "(a) whether it was effective when administered by inhalation, and the effective dose . . . (b) whether it was a substance procurable in reasonable supply (c) its effects on a troop of men in a military context, and (d) means of defence aginst its use."

Clearly, such field trials of incapacitants were a major departure for the program.

Table 2A: Lines of Intramural Research*

1. Oripavine (TL.2636)

Efforts are being made to synthesise simpler, but closely related compounds having the same type of activity...Biochemical studies are in progress to determine the mode of action of compounds of this type.

2. Tremoram Series

Work...has been directed towards elucidating their mode of action and determining the type of chemical structure required for maximum activity.

3. Mental Incapacitant LSD25

Experiments...have included a small scale field exercise (Moneybags).

4. Other potential incapacitating agents

Work...continuing includes that on the indoles, indoline and pyrimidine series of compounds. Naturally-occuring materials are also explored as possible sources of highly active compounds.

* From reference[93]

Table 2B: Lines of Extramural Research*

Professor Olli (Sheffield University)

Natural Products

Professor Rydon (Exeter University)

Ricin

Professor Thompson (Guy's Hospital Medical School)

Snake venoms

Professor Tatlow (Birmingham University)

Hydrocarbons containing fluorine

Dr. Mary Pickford (Edinburgh University)

Synthetic peptides

Professor Williams (St. Mary's Hospital Medical School)

Liver metabolism of drugs (effects of various substances)

Professor Wilson (Liverpool University)

Ultramicro methods of carrying out biochemical studies on drugs

* From reference[93]

1966

The Chemical Defence Advisory Board visited CDEE in June 1966. Mr. Haddon, the CDEE Director, told them that CDEE reported to the Master-General of the Ordnance and, on scientific issues, to the Chief Scientist (Army).[96] The total staff of CDEE was about 900 people. There were 71 approved Scientific Officer, three Medical Officer (Research), 120 Experimental Officer and eight Engineer posts. The United States appointed a full-time Liaison Officer to work at Porton. The main areas of investigation in CDEE's research program were set out in the 1966 Annual Review.[97] These included, within Operational Assessment, studying "the operational effectiveness of incapacitating agents." According to the chair of the Board, new agent research occupied about one fifth of the Establishment's research effort.[98]

In his presentation to the Board, during their June 1966 visit, Dr. Bebbington summarised how work had been narrowed down:[99]

> "four main types of drug effect should be examined in detail at this stage. The fields chosen were *those drugs affecting cholinergic systems, including the psychotomimetic anticholinergics; those affecting adrenergic systems; those, mainly morphine-like, causing depression of the central nervous system; and those, other than anticholinergics, having psychotomimetic properties*" (emphasis added).

Of course, as has been described in detail by Evans,[100] there was a considerable emphasis at this time on studies of the effects of LSD,[101] including another field experiment called Recount.[102]

A 6th Progress Report on Chemical Research on Toxic Compounds by R. R. Hunt[103] was presented to the 53rd meeting of the Chemistry Committee at Porton on 30 June 1966.[104] The work covered by the report was for the period from the previous report in March 1963. The 1966 report began by stating clearly that "[T]he current approach to the research on biologically active compounds is based as far as possible on studies of the mode of action of drugs at the molecular level." Two reports in the open literature[105,106] covered the work on oxotremorine and the investigation of the structure of the muscarinic receptor. Confirming Bebbington's earlier presentation to the board, the report stated that four main types of activity had been chosen for study: cholinergic and anticholinergic activity; catecholamine [adrenergic] depletion; CNS depression; and psychotomimetic activity. Respiratory irritation was also covered in the report but is not relevant here. What is perhaps of most interest is the appearance of glycollates under the category of cholinergic and anticholinergic compounds on which work was being carried out.

The drive towards molecular studies was emphasised in comments made on the CDEE Annual Report by Professor R. B. Fisher, chair of the Chemical Defence Advisory Board.[107] Fisher noted that new agent research accounted for 15 per cent of CDEE's total activity and 20 per cent of all its research activity. However, it seemed to him that with

some regularity the first lead in a new class of compound was found to be the most effective when many modifications were synthesised. He asked:

> "1. Is it possible that, if more time were devoted to determination of the site of action, subsequent synthetic work could be more profitably directed?"

and:

> "2. Is it possible that a review of the modes of action of very highly toxic substances could give help in the search for further such substances?"

In effect, the chair of the board appeared to be asking if the research program was misguided in being too directed towards manipulation of the chemistry of potential agents rather than towards understanding of the receptor that was the target of the agent.

Moves towards a more systematic approach can clearly be seen in the 1966 Porton Technical Papers, for example in an attempt to develop a model that would predict biological activity.[108] More significantly, amongst a series of Porton Technical Papers on the pharmacology of various groups of chemicals (939, 942, 955), one concerning the "Pharmacology of Some Anticholinergic Drugs," Porton Technical Paper 959,[109] was stated to be the first in a series dealing with this subject.

1967

The studies on incapacitants carried out by CDEE were not done in isolation from the armed services. Mr. Gadsby, Director, Biological and Chemical Defence, told the 42nd meeting of the Advisory Council on Scientific and Technological Development[110] that "the Services attached great importance to requirements identified with the feasibility of incapacitating agents," and at the 65th meeting of the Chemical Defence Advisory Board[111] Wing Commander Hampton commented that "the R. A. F. were concerned about the possibility that drugs of this type could be used to 'knock out' an airfield without destroying the facilities." At the 66th meeting of the board Colonel Nicholson[112] noted the offensive requirement that the Combat Development Directorate had advised, that "the ultimate requirement should be for a range of incapacitating agents giving a variety of onset times and durations of effect."

What this might mean, in part, may be gathered from a presentation on "Anticholinergics" given by R. W. Brimblecombe[113] to the 2nd Joint Meeting of the Biology Committee and the Chemistry Committee. He stated that "[E]ffects referred to as long duration would persist for 3 to 5 days, those of intermediate duration about one day, and short acting effects for 2 to 5 hours." Given the perceived importance of chemical warfare and defence, it is not surprising that Mr. Gadsby reported that the ongoing review of defence expenditure would only result in a a small cut being imposed on CDEE,[114] and later,[115] that there would be a reduction of 12 to 13 White Paper (research) Grades by 1971 and that "at this juncture it was not anticipated that this would generate any dramatic problems."

The 4th meeting of the Applied Biology Committee[116] considered a series of papers on the ongoing incapacitants program which give an impression of the changing nature of the program in mid-1967. The papers were: a progress report on work with T.3456 [LSD]; a report of US experience with BZ and other benzilates and glycollates; a report of early exploratory work with BZ in the UK; and a report on future plans for work in the UK [on glycollates]. In regard to the American experience with BZ, Moyland-Jones[117] stated:

> "The glycollates are glycollic acid esters, benzilates being glycollates containing two phenyl rings, while most of the other glycollates of interest contain one phenyl and one other group."

He went on to explain that the pharmacological action of these compounds is anticholinergic, and that incapacitation results:

> "(a) from the peripheral manifestations notably some ataxia and muscle 'tiredness', mydriasis and failure of accommodation and (b) from central effects which present a toxic confusional psychosis."

The severity and duration of the effects depended on the type of glycollate, the dose and the route of administration. All were effective by inhalation, and those which were liquid were active percutaneously.

Moyland-Jones went on to state that US work was directed to "finding a compound more active than BZ, but with a shorter time of onset of effects and shorter duration of activity." He gave a table of compounds with ascending order of duration of effects and argued that EA3580 was most likely to warrant further investigation and it was also active percutaneously.

Kemp's paper[118] on "Future Plans for Work in the UK" added that the US was giving priority to four glycollates, "T.3437, with an onset time of about two hours, T.3126, T.2532 (BZ) and EA3167 which has a long onset time and may produce effects lasting up to three weeks." The UK did not intend to duplicate US work but in view of discrepancies between US and UK studies it would carry out further work on BZ. Additionally, the New Agent Committee had selected two other glycollates for early study:

> "(i) T.3437, chosen for its quick onset of activity and its short duration of effect.
> (ii) T.3436 a compound with intermediate onset time and intermediate duration of effects (as suggested by experiments with animals)."

Porton Technical Paper 959[119] had concluded, from detailed study of 19 compounds, that "T3436 . . . a compound with high activity, a low ratio between peripheral and central activity and an action which is rapid in onset but short in duration might satisfy many of the requirements for a mental incapacitating agent"(emphasis added). The Committee also considered a long paper by Brimblecombe, Beswick and Downing, which

attempted a very wide-ranging survey of possible sources for new ideas on incapacitants such as data on toxic hazards in industry and on old discarded CW agents which had previously only been of interest for their possible lethal effects.[120]

Amongst other reports received by the committees one on "The anticholinergic properties of enantiomeric glycollates" by Brimblecombe and Inch,[121] and the associated Porton Technical Paper[122] were of interest in exploring more deeply how drugs and receptors interacted. Other more detailed work on receptor/drug interactions was reported in regard to morphine-like receptors[123] and in both the then closed[124] and open[125] literature in regard to cholinergic receptors and interactions. An interesting illustration of the increasing sophistication of the work was the development of a radio-transmitter (Figure 1) system to monitor cat brain signals during free-ranging behaviour.[126]

1968

The CDEE Annual Report for 1967-1968 reviewed the ongoing work on synthesis and biological investigation of potential agents and also reported the purchase of more advanced automated apparatus for carrying out the animal testing.[127] However, Dr. Wilson (Chief Scientist, Army) reported to the Advisory Council in October[128] that "the situation might be reaching the point at which it would have to be accepted that the volunteer system had broken down." In that event a service detachment might have to be posted to Porton for testing for one or two months as was done in the United States. Concerns were also expressed over the bad publicity Porton had recently received.

Even more seriously, at the 50th meeting of the Council[129] Mr. Gadsby said "it was important to note that, in keeping with the defence policy of reducing expenditure, CDEE had to achieve a cut of £150,000 in annual expenditure by the financial year 1970-1971." It also had to cut White Paper Grades by one and a half per cent per year for three years. This, he said, would affect the program and, for example, "less effort would be devoted to the search for new incapacitating agents." The structure of the Advisory Committee system was also being reviewed and the annual report of the Council noted that it would be replaced by a new Scientific Advisory Council.[130] However, the report concluded that work on enantiomeric glycollates should be "vigorously pursued." No further trials were required on LSD as it was "unlikely to be used as a C.W. agent." Moreover, as Dr. Barrass explained to the Chemistry Committee,[131] "little attention had so far been paid to elucidating the mode of action of hallucinogens such as LSD-25 and mescaline." Dr. Beswick explained to the Applied Biology Committee[132] that T.3456 (LSD) was not a practical agent because "[T]here were problems of dissemination, the 100% effective dose by inhalation was relatively high, and the material was expensive." In a report on the 6th meeting of the Applied Biology Committee the Chemical Defence Advisory Board[133] heard that the third field experiment with LSD (Small Change) had been satisfactory, but that "work on TL.2636 (an oripavine derivative) was of academic interest only."

Despite such setbacks, a Joint Meeting of the Applied Biology Committee and the Biology Committee in late 1968[134] took the form of an extended seminar on "Behavioural

Studies" with papers on the study of the effects of psychoactive drugs on animals and human beings, the use of electroencephalographical and neurophysiological techniques, the behavioural effects of glycollates and so on. Indeed, work was clearly pressing ahead still with studies of glycollates at this stage.[135,136,137,138]

Assessment

Nevertheless, in a paper for the Offensive Evaluation Committee, Professor Fisher stated:[139]

> "On general grounds I think it unlikely that . . . a pure incapacitator agent will emerge. Any chemical agent, a small dose of which is capable of profound disturbance of bodily or mental funtion, is certain to be able to cause death in large dose . . . and no attack with a chemical warfare agent is likely to be designed with the primary objective of avoiding overhitting."

Professor Fisher's point was much later amply demonstrated, for agents of the Cold War era, by the consequences of using a fentanyl derivative to break the Moscow theatre hostage crisis in 2001.[140] Professor Fisher was more scathing in a paper[141] circulated to all of the committees of the Advisory Board in which he stated that: "The notion of an incapacitator is a little more magical than scientific."

Work on these agents clearly continued at least into the early 1970s in the United Kingdom.[142,143] Yet on the available evidence it seems clear that the UK's search for a chemical incapacitant in the 1960s was unsuccessful. Whether a similar search today would have the same result is unclear in view of the great advances that have been made in our understanding of the nervous system, and particularly the structure of receptors for neurotransmitters.

*This is an extended version of the first section of the chapter on Midspectrum Incapacitant Programs in *Deadly Cultures* (Ed. Wheelis *et al*), Harvard University Press, 2005.

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